THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

NOVEMBER, 1921

ORIGINAL ARTICLES.

THE PATHWAYS OF INFECTION IN THE NERVOUS SYSTEM.

A PRESIDENTIAL ADDRESS TO THE NEW YORK NEUROLOGICAL SOCIETY.[1]

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Something less than eleven years ago I came to New York to undertake the duties of chief of clinic at the Neurological Institute. I had then a few American friends, whom I had made in London, but none were here; yet the amazing kindness of this country has since made the number of my friends here legion, and the honor you have done in making me your president is an index of the generosity and gentleness of your hearts toward those of different antecedents and training from yourselves.

There is a host of resemblances in the customs of the two great branches of the English-speaking peoples, but one might say with justice that the attitude toward the stranger differs on the two sides of the Atlantic—in Great Britain he is to be viewed socially with suspicion until he proves himself innocent, while in this kindly country he is accepted at something more than his face value until his actions betray him. It is a nice point, therefore, whether my position in this honorable society is to be attributed to my subtlety or to your goodness, nor should I wish for personal reasons to press these researches too closely. Instead I thank you in all gravity

[1] Delivered February 1, 1921.

for the trust you have shown me, which I shall do what in me lies to deserve.

A few weeks ago there was held a meeting of the newborn Association for Research in Nervous and Mental Diseases, an organization fathered by this society, which will be regarded, we trust, in the next couple of decades as a really constructive effort in our branch of medicine. In this concerted attempt to investigate thoroughly a single disease picture, we discovered our strength as clinical observers and as pathological anatomists, and our need of aid from those with knowledge in other fields than our own. From the collected evidence, we gleaned the idea that epidemic encephalitis was an organismal reaction rather than a specific clinical entity; that its picture was drawn and colored probably more by the physiological function of the structure attacked than by the specificity of the virus. We examined carefully the morbid tissues of fatal cases; we explored the battlefields, but made little mention of the roads by which those stricken places were reached by the invading armies. We found that the bulk of individuals with encephalitis had evidence of an injury to the mesencephelon, to the striate bodies and to the red nucleus; we found that, most usually, the first sign of infection other than general malaise was diplopia dependent on a disintegration of function in the oculomotor nuclei, a district at first sight not easily accessible to exogenous poisons. Without speculation on this anomaly of disease incidence, those of us, who consciously deliberated on this phenomenon at all, were content weakly to ascribe to the poison, or group of poisons, responsible for the disease, unknown properties of specific chemiotropism for the nerve structures initially damaged.

This has seemed to me, therefore, an appropriate occasion on which to examine, even without detail, some of our knowledge regarding the routes by which bacteria and toxins, organic and inorganic, can achieve admission to the highways and byways of the central nervous system. In doing so, I cannot hope to tell you any new thing, but rather to refresh your memories of work done in the past and overlain by the accumulations of more recent times. It is well occasionally that we take stock of our possessions; those we have had for long grow dusty and unrecognizable, and we often fail to see how they complement and illumine our baubles acquired but yesterday. The Minotaur was found and slain in the labyrinth only by the aid of Ariadne's guiding threads, and in our searchings we must see to it that some of these be held unbroken.

The bases of our knowledge of the properties of nervous tissue, laid down almost entirely in the lifetime of our senior members, were of necessity anatomical and physiological. The notion of the ancients had to be dispelled—not so many centuries ago—that the purpose of the brain was but to cool the hot and noisome vapors

arising from the heart! Analysis of centers, tracts and functions have given us a storehouse of knowledge incredibly large indeed, when one considers the short time that has elapsed since groups of men seriously began to apply themselves to neurological problems. When, however, these were beginning to be solved little or nothing was known of infection, bacteriology was still unborn, and to explain morbid processes, men were oriented toward innate degeneration and deficiency of vital forces rather than to the guerrilla warfare, which we now know to be waged unceasingly in our bodies, between our cells and humors on the one hand and an implacable host of microscopic and ultramicroscopic organisms on the other.

The assumption of death of specific tracts and centers before the rest of the organism, of a simple vital lack in a few cells or fibers satisfied us when we were unconscious of the roles capable of being played by insidious infections; so amyotrophic lateral sclerosis, among other ills, was explained by an abacadabra charm called abiotrophy, and the great group of the myopathies was similarly incanted, though we feel ourselves now on the threshold of knowledge of their morbid courses by the portal of the endocrines.

In the presence of your retiring president it might be an impropriety in me to dilate much on this last notion, but I may submit that a consideration of the pathogenesis of the infections of the nervous system may reveal a unity of morbid process in many ailments clinically unlike, a pathological synthesis at least as valuable as the meticulous analyses of symptoms to which we have been accustomed to bend our minds.

The reaction of each of us to a given infection varies (could we but notice the variations) with the different physical personalities which we possess; perhaps—though this is a seven-league step—with the different kinds of endocrine balance in each of us! Our senses require training to detect differences between similar-appearing objects; I remember my difficulty in Russia in distinguishing one acquaintance from another, and on my return, for the first few days the feeling that I knew all the passers-by on a London street because of their general racial and facial resemblance to my friends and relations. So I believe that in the future we shall be able to perceive small individual reactions to toxins from without, reactions which we now look at but do not see. Further, just as one man differs from another in his reaction to infection, so in a single organism there is a host of unknown and little thought of circumstances which determine the incidence and distribution of the lesions—a case of Addison's disease has tuberculosis of the adrenal glands, but one would like to know why he has not a tabes mesenterica or a fibroid phthisis instead.

But such problems at present are merely exasperating, though they will be solved, and some, not improbably, in our day. A

statement of such an example, however, shows our modern wish to be dissatisfied with the mere nomenclature of disease and our desire to dig into the basic study of the conditions of liability and resistance to infection in the various tissues and organs of the body.

The sentry guarding the gate by which infections most commonly reach the central nervous system is the cilia of the mucosa of the airways and especially, perhaps, the mucoid material with which the mucosa is lined. Bayliss has stated that it is mucin which protects the digestive tract from the effects of its own juices, and it is likely that ferment action from dead or living bacteria effects the first rent in the epithelium, giving access therefrom to the lymphatic and blood systems. Benians has demonstrated that Shiga's bacillus can be held alive and harmless in the organism for months if surrounded by mucilage of tragacanth, and this without the production of antibodies in the host against the bacillus. It has been shown that bacteria in carriers are always interned in a mass of mucus, nor have carriers usually developed an active immunity against their potential parasite. In the British training camps and barracks an unduly high carrier rate for the meningococcus invariably preceded the outbreak of an epidemic of cerebrospinal fever, and a task still to be done would be to discover if there be any relationship between susceptibility to infection and nasopharyngeal disease, involving a defect of mucoid secretion—an objective to be gained not alone in cerebrospinal fever but in epidemic encephalitis and poliomyelitis as well.

I have just said that epithelial destruction of mucous membrane is the prelude to invasion of the lymphatic and blood systems by bacteria and their toxins; over the respective roles of these two systems, in conveying noxious material to the nervous system, much recrimination has occurred. As in most controversies there is some truth on both sides, but I believe that an examination of the evidence will in our day dispose of neutrality of thought in the matter. Despite the state of philosophic doubt in the minds of Alford and Schwab, it would appear that the defensive mechanism of the choroid gland in excluding all hematogenous material unsuited to its purpose coupled with the anatomical continuity of the lymph system with the cerebrospinal pons—a continuity accepted by such observers as Halliburton and Starling—make it more than a working hypothesis that, by the perineural and endoneural lymph channels of the cranial and spinal nerves, toxins can reach with unfortunate ease the cerebrospinal axis.

Twenty years ago experimenters were struck by their utter failure to produce characteristic brain and cord lesions by the intravenous injection of bacteria of high virulence; we are now aware of the role played in elective filtration, to use Mestrezat's phrase, by the choroid plexus, whereby large colloid molecules are forbidden access to central nervous tissue—the whole group of

albumenoid toxins are thus cut off from direct invasion of the brain space; I have said *direct* invasion for these large molecules can pass easily through the walls of the capillary vessels, so breaking from the blood to the lymphatic economy. This permeability of the capillary wall is an important factor in the mechanism of many of our infections; Marie, confirmed by Meyer and Ransome, showed that tetanus toxin passed to the lymph vessels from the initial lesion, thence to the blood, thence to the motor end-plates, thence by efferent nerves to the spinal cord—and it has further been shown that if these same nerves be cut an otherwise lethal dose of tetanus can be given without any cord involvement at all; the incubation period in experimental tetanus varies in warm-blooded animals with the length of peripheral nerve tissue to be traversed, a few hours in rats to several days in the horse. When the lower segments of the cord were already the seat of experimental tetanic irritation, it has been always possible to prevent cervical implication by dorsal section, and it is interesting to note, further, that dolorous tetanus, produced by the injection of the posterior roots proximal to the ganglia, was in no instance accompanied by any sign of ventral horn irritation.

However, tetanus intoxication takes place through both the blood and lymph systems, and in experimental intoxication the poison can be demonstrated in the blood even in the earliest stages, but in a state of high dilution; it reaches the subarachnoid spaces of the lumbar enlargement in a much higher concentration through the lymph spaces of the peripheral nerves. One must notice, however, that trismus is one of the earliest signs of the onset of generalized tetanus even when the initial lesion has been in one of the lower extremities. This would seem to be an evidence of a blood-borne toxemia, though the mechanism by which the motor root of the fifth nerve is thus early irritated is by no means clear.

Might I bring to your attention in this connection that in diphtheritic nerve intoxication oculomotor palsy is a constant feature of the disease wherever the infecting focus may be in the body, and we have referred already to the very usual early infection of the third nerve nuclei in epidemic encephalitis. This special susceptibility, to react to general infection on the part of the mesencephalic nucleus of the motor fifth nerve and on the part of the mesencephalic oculomotor nuclei, may not be due simply to an undue delicacy of these structures but may depend on anatomical avenues for invasion as yet not comprehended.

A consideration of the mass of diphtheritic infections occurring in the course of the Palestine campaign has led Walsh away from the idea that this virus is exclusively blood-borne with special affinity for discrete areas of nerve tissue, and toward a notion of the part played by the process named by Orr and Rows lymphogenous toxi-infection of the nervous system. Among the troops operating against the Turks there was an outbreak of so-

called desert sores, which in certain units of the Egyptian expeditionary forces affected 40 per cent of the men. These sores were thought to have some connection with the horse manure laid down on the desert roads, for they ceased to be a military anxiety when the army had attained the fertile plain of the Promised Land. From almost all of these sluggish ulcers Klebs-Loeffler bacilli were recovered in nearly pure culture, and a vast number of cases of peripheral neuritis ensued. The most important observation made by Walsh on this material was that invariably there was an initial local paresis related anatomically to the site of the infective focus—a circumstance in itself disposing of the idea that in such conditions the poison is entirely carried by the blood to the nervous elements; the poliomyelitic virulence of the mesenteric lymph glands of subjects, whose blood is innocuous, is another circumstance of moment in the same connection. At least two of these diphtheritic cases should be quoted here briefly: One, an artillery driver, who suffered from multiple septic sores on the thighs and buttocks and a large ulcer in the perineum also of ten weeks' duration. In the seventh week of his illness he began to experience numbness around the anus and on the buttocks. This sensation of deadness spread to the penis, scrotum, and to the backs of the thighs; a few days later there was loss of control of the bladder and rectum. Not for weeks after the appearance of these conditions did the signs and symptoms of a mild subacute toxic polyneuritis occur, by which time there was also a ready fatigue of visual accommodation. On examination, this man was found to have complete loss to all forms of sensation over the skin areas supplied by the fourth and fifth sacral roots and severe loss of sensibility over the second and third sacral root areas. It was noticed that the segmental symptoms were improving *pari passu*, with an increase in those referable to the terminal nerve twigs.

The second case I ask your leave to quote is that of a medical officer, who infected his right thumb when performing a tracheotomy upon a fatal case of laryngeal diphtheria. In seven weeks the digital wound had healed, but he began to notice numbness and loss of feeling in the affected thumb, signs and symptoms which spread to the radial part of the hand and subsequently were present in the entire hand and forearm. At the same time ataxia and loss of power developed in the right upper extremity. After these disabilities had occurred in the limb he sustained a generalized multiple neuritis, but did not experience accommodation paralysis.

Neither of these patients had any affection of the palate, in which circumstance they were identical with the other cases of paralysis following extrafaucial diphtheria.

Perhaps I might be allowed to correlate with this material, those cases described by myself as acute infective neuronitis. These occurred as a minor epidemic among soldiers in the field and were characterized by fever, peripheral neuritis and ascending signs of

involvement of the spinal roots and ganglia. In some of them the posterior roots suffered vastly more than the peripheral nerves, so that root zones of grossly altered sensibility were easily demonstrated. A constant feature of these cases was peripheral paralysis of the face and the lower muscles of deglutition. The pathological picture produced was extraordinarily akin to those obtained experimentally by Orr and Rows in their work on lymphogenous infections and the gross involvement of the spinal ganglia in my cases gives point to the suggestion that these structures may act as blocks to the centripetal transportation of lymphogenous poisons.

Severe damage to the cells of the posterior ganglia was a feature also of a series of ascending neuritides of the cauda equina, which I described with Charles Elsberg in 1913, and the arguments for the lymphogenous nature of the virus in tabes through the changes in the dorsal root entry zone are sufficiently familiar to warrant no more than a passing mention in an address already growing overlong. We should notice, however, the interesting fact that degeneration of exogenous fibers invariably begins at the point where the neurilemma leaves off and that, in fatal cases of diphtheritic poisoning, where the palate has been entirely disabled, the vagal nuclei have been found destroyed without any evidence of injury to the vagi themselves. Whether the influence of the neurilemma on the axis-cylinder be protective or nutritive, whether it be vital or mechanical or whether its role is an integral part of neural conduction is one of the major problems of neurology today. Before turning from these surface speculations on some of the avenues of infection of the central axis, we should refer suggestively to Collins and Armour's autopsied case of acute bulbar palsy in a child with mumps; and especially to a series of cases described by Wilfred Harris of chronic bulbar palsy immediately following diphtheria, clinically resembling myasthenia gravis, but differing from that condition by the absence of ptosis, dyspnea or variability of disease picture, and by the presence of muscular atrophy and the reaction of degeneration. Dr. Dana has described amyotrophic lateral sclerosis directly produced by lues; a group of patients with chronic lead poisoning suffering from the same disease has come under my own observation, and Stanley Barnes has recorded a number of patients with a chronic toxic affection of the lower motor neurone, having a tendency to slow improvement following acute specific fevers.

It is fair to suppose, therefore, that further investigation of the routes, by which infections attain the brain and cord, may reveal much regarding the pathogenesis of some nervous ailments. We can hope, however, to illuminate only a few problems by any one method. Thus an attempt, and one somehow appealing, has been made recently to show that the location of the lesion in the combined spinal sclerosis of anemia and marasmus depends ultimately on a depreciated adrenal activity operating on the spinal pial ves-

sels through the thoracicolumbar sympathetic chain. One may add that some such synthetic imagining is required to account for the so-frequent incidence of spinal tuberculosis in the fifth or sixth dorsal vertebræ. The clinical phenomena of acute multiple sclerosis suggest a perivascular outpouring of fluid into the nervous elements, to study which adequately requires more than a notion of the conditions governing osmotic pressures in living organisms, and possibly also of colloidal chemistry and the specific action of calcium ions in producing abnormal permeability of capillary vessels. Indeed, the whole question of radio-active salts on cell function might well have to be determined before a satisfactory explanation of such a well-recognized clinical process as I have just mentioned can be forthcoming.

The development of all branches of medicine has led to diversion of talent into a variety of areas as separated from each other as though each observer were in a kite balloon by himself—nor have we evolved any adequate headquarters where reports from each can be received and correlated. The modern student receives instruction in animal physiology from physiologists who never enter a ward, in chemistry from chemists often without interest in either physics or biology; structure and function in his mind are in different water-tight compartments so that in the beginning of his clinical years he is in travail to apply his knowledge to the problems before him, and must needs explain a hemianopia by a possible lesion of the bundle of Vicq d'Azyr. The same segregation of different branches of knowledge is continued into our adult professional lives. As a society for the advancement of learning we must try to arouse interest in our problems among physiologists and biological chemists, among pathologists and anatomists; we should seek to include them in our body. Their science would be more humane, our medicine more scientific. I should go even further than this, for I can see no disability but a great gain, through a new orientation, if sometimes we were to choose to lead us, a man, not of our specialty, but one of erudition in some cognate sphere, with sympathy for our state of darkness. No one can play equally sweetly on all the instruments of an orchestra and the conductor should be changed with the kind of music to be played.

In all civilizations known to us there has been a fairly regular sequence in the flowering of thought: First, there develops carving and painting and building as expressions of the human spirit, then comes literature and, last of all, science strides forward. For us, this last cycle is but beginning, and there will be time enough before the great changes are rung in the world to lay down principles, the knowledge of which may with fortune be stored up for the peoples who will come after ours. Let there be but coöperation among all kinds of us and then, "Turn you to any cause of policy, The Gordian knot of it you will unloose, Familiar as your garter."

THE EFFECT OF TREATMENT FOR SYPHILIS ON SEVERE ANEMIAS

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FOURNIER in reviewing the anemias of syphilis states that the disease causes a diminution in the percentage of hemoglobin, a decrease in the number of erythrocytes and an increase in the number of leukocytes. He recognizes five types of anemia in association with the disease: (1) the simple secondary anemia (by far the most common), (2) chlorotic anemia, (3) chlorotic anemia with leukocytosis, (4) leukemia and (5) (infinitely rare) syphilis imitating the picture of pernicious anemia.

Fournier refers to the difficulty in some cases of deciding whether syphilis is the direct cause of these modifications or whether they are the result of associated symptoms (the febrile state, symptoms of dyspepsia, nervous troubles, superimposed infections or the influence of misguided therapy). He quotes the old saying that "mercury is the iron of syphilitic anemia." However, after having corrected the syphilitic changes, mercury becomes, in turn, an alterant of the blood. For a time it does good, later it becomes harmful. Mercury cannot be given over a prolonged period without damage. Fournier instituted, therefore, the "method of successive or intermittent treatments."

Since Fournier's time little has been added to our knowledge of the mercurial therapy of syphilitic anemias. The advent of arsphenamin has brought new possibilities, which, although extensively discussed in the abstract, have been reinforced by only a small body of clinical material. This paucity of clinical discussion may be ascribable to the comparative rarity of pernicious anemia in combination with syphilis. The total number of cases with or without syphilis treated with arsphenamin which have been collected from the literature is thirty-six. To this are now added the twenty-five cases of severe anemia which form the basis of the present study. Primary emphasis is laid on the effect of arsphenamin therapy, since the cases were originally approached from this angle.

REVIEW OF LITERATURE

Arsenic was first used in treating pernicious anemia with gratifying results in 1875 by Bramwell. In 1911 he began using arsphen-